MILLENNIUM

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6th July, 2005

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Re: Draft Guidance for Industry: Exploratory Investigational New Drug Studies.
[Docket No. 2005D-0122, 70 *Federal Register*, 19764-19765, April 14, 2005]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. ("Millennium"), a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN® (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE™ (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium warmly welcomes FDA's publication of draft guidance on exploratory Investigational New Drug applications (exploratory INDs) as a rational and powerful means to improve the efficiency of the selection of drug candidates during the phase of drug discovery that has been termed "lead optimization". We wish to make four specific comments.

1. We note that the draft guidance generally does not address issues related to exploratory studies with proteins or other complex macromolecules. There are important differences in the types of data to be provided for small molecule chemical drugs, both in respect of pre-clinical testing and safety studies and chemistry, manufacturing and controls data. We strongly suggest that data requirements for large molecules are included in the final guidance.

2005D-0122 C3

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2. Lines 257-258 – The sponsor is required to provide information showing the stability of the test article during the toxicology studies, but no specific duration of stability testing is mentioned. Applicants are referred to earlier FDA guidance[1] that also does not mandate any set period of stability testing, but has the following statement (Section IIIF): *For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.* We would assume, therefore, that it will be generally acceptable for investigational material that is used in toxicology studies to have no pre-existing stability data, if the batch used is found to be within specifications immediately before and immediately after the dosing period. If this is the case, we suggest that it would be helpful if this were explicitly indicated in the guidance. If this is not the case, and a longer duration of stability must be shown, then we suggest that this, too, should be indicated in the guidance, together with an explanation of the need for the longer duration. As noted in the guidance document, we eagerly await publication of the draft companion guidance document on lab-scale GMP considerations.

3. Lines 417 – 424 - We note that FDA indicates in the draft guidance that it will be prepared to be, to some degree, flexible with regard to the requirement for all data presented in an exploratory IND to have been generated under full Good Laboratory Practices (GLPs). In the spirit of making the exploratory IND as powerful a source of time and resource efficiency as possible, we suggest that many of these pre-development studies, if conducted in the "spirit of the GLPs" (i.e., done with appropriate control and anlyses but not with minutely detailed volumes of documents) could be used to support early human trials. Therefore, we would recommend that the Agency should remove the general requirement for studies submitted in an exploratory IND to have been conducted under GLP's, provided that they have been well designed and conducted, and the data are sufficiently robust to support the proposed trials. We believe that the removal of this restriction is justified because it would allow significant working efficiencies and because all compounds that progress to full clinical development will be supported, in any case, by a full IND application with the required GLP studies. As a corollary to lifting the general requirement for data to have been generated under GLPs, we would suggest that FDA should indicate more specifically those types of studies for which formal compliance with GLP will be essential.

4. Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), drug sponsors' patents may be restored by a period equal to half of the interval between the filing of an IND and the submission of an NDA (the "development period"), plus a period equal to the interval between the submission of the NDA and FDA's approval (the "review period")[2]. It is clear that

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[1] *Guidance for Industry: Content and Format of Investigational New Drug Applications for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.*

[2] 35USC156

exploratory INDs are legal exemptions given to drugs for research purposes[3] and that, as such, when sponsors file an exploratory IND for a drug before they open a full IND, the start of the development period should be dated from the filing the exploratory IND, for the purpose of calculating the duration of patent restoration. We recommend that FDA should clarify this in the guidance.

We appreciate the opportunity to comment on this important report and look forward to working with FDA to realize its potential.

Sincerely,

Robert G. Pietrusko, Pharm.D.,
Senior Vice-President, Worldwide Regulatory Affairs,
Millennium Pharmaceuticals, Inc

[3] 21USC355(i)